Remarks

Favorable reconsideration in view of the herewith presented amendment and remarks is respectfully requested.

In accordance with the Examiner's request, attached hereto is a clear copy of claims 1 to 8 as originally filed.

The trademark COSTAR as it appears on page 10 of the application has been acknowledged.

Claims 1 to 8 have been rejected under 35 USC §112, second paragraph as allegedly being indefinite.

Applicants respectfully traverse this rejection.

The term "substantially" is widely used in patents, including those relating to inventions from the life sciences field. As such, the term "substantially free of..." as used in present claim 1 would be readily understood by a person skilled in the art as meaning "free or almost free". Applicants submit that the inclusion of this wording does not lead to inclarity, but rather merely reflects the physical reality, as understood by persons skilled in the art, that in terms of treating natural materials, it is increasingly difficult to exact all of anything from them.

This was seemingly appreciated by the USPTO during the prosecution of the applicants' earlier US patent number 5,397,353, as cited in the specification of the present application. Granted claim 1 of this earlier patent includes the wording "... is substantially free of non-fibrous tissue proteins and glycoproteins, is substantially free of

cellular elements, is substantially free of lipids and lipid residues...". It is respectfully urged that "substantially free of" does not render present claim 1 unclear.

The recitation of "sufficiently large" is no longer used to define the composition of claim 1 as amended, and the Examiner's objection in this regard is therefore moot.

Applicants urge that the term "pasty" is not, in fact, unclear. Applicants enclose a copy of the relevant section of the Concise Oxford Dictionary (Tenth Edition), Oxford University Press, Oxford, UK, 1999 (Enclosure 1). The word "pasty" means "of or like paste" and "paste" means "a thick, soft, moist substance". These terms would be clear to a person skilled in the art.

Moreover, the specification of the present application teaches that a starting material can be reduced "from large pieces to small particles which can then be formulated into a sterile injectable composition or a sterile wound filling paste" (page 5, lines 32-34; emphasis added).

The specification continues, "In order to produce a collagen paste with appropriate density and rheological properties (flow rate and an ability to retain shape after moulding), a suspension of collagenous particles in a suitable carrier an be prepared to form a controllable concentration of the composition" (page 5, line 36 to page 6, line 5).

Further, at page 7, lines 8-10 of the specification, it is disclosed that "in the pasty wound filling compositions, the concentration of solids is generally up to 80%".

Uses of pasty compositions according to the present invention are described at page 9, lines 10 to 28 of the specification.

Thus, applicants urge that the meaning of "pasty" as used in claim 8 of the present application does not in fact render this claim indefinite, the term being perfectly clear to one skilled in the art and being used throughout the specification in its usual sense.

For the above reasons, applicants request reconsideration and withdrawal of the §112, second paragraph rejection.

Claims 1-3 and 5-8 have been rejected under 35 USC §102(b) as allegedly being anticipated by Wallace *et al.* (Wallace).

Claims 1-3 and 5-8 have been rejected under 35 USC §102(b) as allegedly being anticipated by Bert *et al.* (Berg).

Claims 1 and 4 have been rejected under 35 USC §102(b) as allegedly being anticipated by Janzen *et al.* (Janzen).

Applicants respectfully disagree with the Examiner as to all of these rejections.

Claim 1 has been amended to distinguish clearly the subject matter of the present invention over the prior art compositions, none of which comprises particles of a collagenous material that "displays the original fibre architecture and molecular ultrastructure of the natural tissue material from which it is derived". support?

None of the cited prior art references anticipates the subject matter of the present invention. Wallace relates to an injectable implant composition consisting of an aqueous suspension of a biomaterial, such as a cross-linked collagen, that includes a fluid lubricant to improve injectability. This reference does not disclose the composition of the present invention, in which particulate collagenous material dispersed in a biocompatible carrier medium must display the original fibre architecture and molecular ultrastructure

of the natural tissue material from which said collagenous material is derived. In fact, Wallace teaches the preferred use of the fibrillar cross-linked collagen of US 4,582,640 (Smestad *et al.*), which was also cited by the Examiner (see page 2, lines 34-36). This fibrillar material is quite distinct from the particulate collagenous material of the present invention, as discussed in further detail below.

Similarly, Janzen and the remaining cited documents all describe solublized and reconstituted collagenous materials prepared in such a way that the original fibre architecture and molecular ultrastructure of the collagen is lost.

The present invention comprises material presented at the fibre fragment level of organisation, as disclosed in the description (see page 4, line 34). As shown in the enclosed diagram (Figure 5-3 from "Basic Histology", Junqueria, L.C. and Carneiro, J., Lange Medical Publications, Los Altos, 1980; page 91) (Enclosure 2), collagen fibres are distinct from their constituent fibrils and the individual protein molecules.

In order to illustrate this point, enclosed are scanning electron micrographs showing particles of collagenous material according to the present invention. (Enclosure 3).

Scanning electron microscopy was carried out on pure samples of milled collagenous material in order to allow visualisation of the fibre fragment structures. The samples were first dried using a Polaron E3000 Series II critical point drying apparatus, and mounted on aluminum stubs using double-sided carbon tabs and coated for 5 minutes using a Polaron E5100 Series II 'cool' sputter coater fitted with an Au/Pd target. Samples were viewed by means of a JEOL JSM-35 scanning electron microscope at an accelerating voltage of 15 kV.

The scanning electron micrographs clearly demonstrate that the particles of collagenous material comprise bundles of fibre fragments free from cellular debris. The original collage fibre architecture and molecular ultrastructure of the natural tissue material from which the collagen particles were derived is clearly retained. Figure A shows mixed fibre fragments, still in bundles after milling (200x magnification). Figure B shows a close-up of a fibre bundle, take at 1200x magnification and the same bundle can be seen in Figure C at a higher (4400x) magnification. The parallel fibres in the bundle are clearly visible. In Figure D, the cut ends of the fibre bundle can be seen.

In contrast to the present invention, the prior art injectable collagen preparations comprise dissociated collagen fibrils or molecules. In order to illustrate the significant difference between the present invention and the prior art, enclosed herewith is an extract from "Collagen, Volume III Biotechnology," Nimni, M.E., Ed., CRC Press, Inc. Boca Raton, 1988. (Enclosure 4). In Chapter 5, at page 118 of this publication, the preparation of an injectable collagen implant ("ZCI") from a soluble collagen intermediate is described. At page 120 of the same publication, this representative prior art injectable collagen is described as being "a highly polydisperse mixture of fibrils" (see paragraph D. "Fibrillar Structure"; emphasis added). An electron micrograph given at page 121 ("Figure 3") shows the suspension of collagen fibrils comprising ZCI. This should be contrasted with the injectable collagenous material of the present invention, which displays the original fibre architecture and molecular ultrastructure of the natural tissue material from which it is derived.

Thus, applicants submit that the claims of the present application are in fact novel over the cited prior art, which describes reconstituted collagen prepared by processes that destroy the original fibre architecture and molecular ultrastructure of the collagen fibres.

Reconsideration and withdrawal of these rejections is respectfully requested.

It is urged that the present application is in condition for allowance. Early and favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

If the Examiner believes that issues may be resolved by telephone interview, the Examiner is respectfully urged to telephone the undersigned at (212) 801-2146. The undersigned may also be contacted by e-mail at ecr@gtlaw.com.

No additional fee is believed to be necessary. The Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 50-1561.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-1561.

Respectfully submitted,

Dated: January 9, 2003

By: _____

Eugene C. Rzucidlo
Registration No. 31,900
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ATTACHMENT A

1. (Amended) An implant composition which comprises a biocompatible carrier medium having dispersed therein particles of collagenous material which are derived from a natural material and the collagenous material displays [where the particles are sufficiently large to preserve] the original architecture and molecular structure of the natural tissue material from which it is [they are] derived and wherein the collagenous material is substantially free of non-fibrous tissue proteins, glycoproteins, cellular elements and lipids or lipid residues and which is non-cytotoxic.

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dehydrated using several changes of 100% ethanol and anhydrous acetone. Using a ball mill, the dried collagen pieces were ground and sieved to produce a fine white powder. The sieved powdered collagen was rehydrated in s sterile phosphate buffered saline to produce a collagen suspension concentration of 60 to 70% (w/v).

Example 2

Small pieces of blotted porcine collagen were frozen in liquid nitrogen and ground in a cryogenic mill. The ground collagen fragments were suspended in sterile phosphate buffered saline to produce a collagen suspension concentration of 60 to 70% (w/v).

Example 3

To directly examine cell/collagen biointeraction, sieved powdered porcine dermal collagen was rehydrated in complete mammalian cell culture medium to produce a collagen suspension concentration of 70% (w/v) and seeded with either primary human foreskin fibroblasts or primary rat skin dermal fibroblasts.

Collagen/fibroblast samples were aliquoted into COSTAR® a registered trademark in relation to cell culture wells and incubated at 37°C, 5 to 7% (w/v) CO_2 saturated humidity. As studied over a 21 day incubation period, both human and rat fibroblasts proliferated and migrated into and adhered to the porcine collagen fragments which they assembled into densely packed clumps or discs.

Example 4

To examine in vivo performance collagen suspensions were injected (0.2 ml/injection through a 21 gauge needle intracutaneously into dorsal sites in isogenic PVG/Ola

1. An implant composition which comprises a biocompatible carrier medium having dispersed therein particles of collagenous material where the particles are sufficiently large to preserve the original architecture and molecular structure of the natural tissue material from which they are derived and wherein the collagenous material is substantially free of non-fibrous tissue proteins, glycoproteins, cellular elements and lipids or lipid residues and which is non-cytotoxic.

2. A composition according to Claim 1 wherein the collagenous material is free or substantially free of antigenic polysaccarides and mucopolysaccharides

3. A composition according to Claim ~~1 or 2~~ wherein the biocampatible medium is saline, dextran solution, or glycerol or a non-toxic antigenic viscous polysaccharide.

4. A composition according to ~~any one of~~ Claim ~~1 to 3~~ wherein the collagenous material contains a proportion of elastin.

5. A composition according to ~~any one~~ Claims 1 ~~to 4~~ wherein the collagenous material is cross-linked.;

6. A composition according to ~~any one~~ Claims 1 ~~to 5~~ wherein the particle size of the particles of collagenous material is within the range of 50 to 500 microns.

7. A composition according to claim 1 ~~any one of the preceding Claims~~ wherein the concentration of solids is to 10 to 70 percent by weight and the consistency of the composition

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is such as to enable it to be administered by injection.

8. A composition according to any one of the preceding claims, wherein the composition is of a pasty consistency.